

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 April 2002 (04.04.2002)

PCT

(10) International Publication Number
WO 02/26825 A2(51) International Patent Classification⁷: C07K 14/705

(21) International Application Number: PCT/US01/30661

(22) International Filing Date:
28 September 2001 (28.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/236,546	29 September 2000 (29.09.2000)	US
60/240,589	13 October 2000 (13.10.2000)	US
60/242,322	20 October 2000 (20.10.2000)	US
60/242,223	20 October 2000 (20.10.2000)	US
60/245,855	3 November 2000 (03.11.2000)	US
60/245,900	3 November 2000 (03.11.2000)	US
60/247,587	9 November 2000 (09.11.2000)	US
60/249,343	15 November 2000 (15.11.2000)	US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: G-PROTEIN COUPLED RECEPTORS

(57) Abstract: The invention provides human G-protein coupled receptors (GCREC) and polynucleotides which identify and encode GCREC. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of GCREC.

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from the group consisting of SEQ ID NO:1-16, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16. The method comprises a) exposing a sample comprising the
5 polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

10 Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid
15 sequence selected from the group consisting of SEQ ID NO:1-16, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a
20 pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional GCREC, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid
25 sequence selected from the group consisting of SEQ ID NO:1-16, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group
30 consisting of SEQ ID NO:1-16. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino
35 acid sequence selected from the group consisting of SEQ ID NO:1-16, b) a polypeptide comprising a

assay may comprise the steps of combining at least one test compound with GCREC, either in solution or affixed to a solid support, and detecting the binding of GCREC to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor.

Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural
5 product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

GCREC of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of GCREC. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for GCREC activity, wherein GCREC is combined with at least one test compound, and the activity of GCREC in
10 the presence of a test compound is compared with the activity of GCREC in the absence of the test compound. A change in the activity of GCREC in the presence of the test compound is indicative of a compound that modulates the activity of GCREC. Alternatively, a test compound is combined with an in vitro or cell-free system comprising GCREC under conditions suitable for GCREC activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of
15 GCREC may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding GCREC or their mammalian homologs may be “knocked out” in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of
20 human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by
25 homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and
30 the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding GCREC may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate
35 into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al.

of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding GCREC and other genes of interest can be analyzed by northern analysis or microarray techniques.

XIV. Production of GCREC Specific Antibodies

GCREC substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the GCREC amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for anti-peptide and anti-GCREC activity by, for example, binding the peptide or GCREC to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XV. Purification of Naturally Occurring GCREC Using Specific Antibodies

Naturally occurring or recombinant GCREC is substantially purified by immunoaffinity chromatography using antibodies specific for GCREC. An immunoaffinity column is constructed by covalently coupling anti-GCREC antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing GCREC are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of GCREC (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/GCREC binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and GCREC is collected.

XVI. Identification of Molecules Which Interact with GCREC

Molecules which interact with GCREC may include agonists and antagonists, as well as

molecules involved in signal transduction, such as G proteins. GCREC, or a fragment thereof, is labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton A.B. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) A fragment of GCREC includes, for example, a fragment comprising one or more of the three extracellular loops, the extracellular N-terminal region, or the third intracellular loop.

- 5 Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled GCREC, washed, and any wells with labeled GCREC complex are assayed. Data obtained using different concentrations of GCREC are used to calculate values for the number, affinity, and association of GCREC with the candidate ligand molecules.

Alternatively, molecules interacting with GCREC are analyzed using the yeast two-hybrid
10 system as described in Fields, S. and O. Song (1989) *Nature* 340:245-246, or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech). GCREC may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S.
15 Patent No. 6,057,101).

Potential GCREC agonists or antagonists may be tested for activation or inhibition of GCREC receptor activity using the assays described in sections XVII and XVIII. Candidate molecules may be selected from known GPCR agonists or antagonists, peptide libraries, or combinatorial chemical libraries.

- 20 Methods for detecting interactions of GCREC with intracellular signal transduction molecules such as G proteins are based on the premise that internal segments or cytoplasmic domains from an orphan G protein-coupled seven transmembrane receptor may be exchanged with the analogous domains of a known G protein-coupled seven transmembrane receptor and used to identify the G-proteins and downstream signaling pathways activated by the orphan receptor domains (Kobilka, B.K.
25 et al. (1988) *Science* 240:1310-1316). In an analogous fashion, domains of the orphan receptor may be cloned as a portion of a fusion protein and used in binding assays to demonstrate interactions with specific G proteins. Studies have shown that the third intracellular loop of G protein-coupled seven transmembrane receptors is important for G protein interaction and signal transduction (Conklin, B.R. et al. (1993) *Cell* 73:631-641). For example, the DNA fragment corresponding to the third intracellular
30 loop of GCREC may be amplified by the polymerase chain reaction (PCR) and subcloned into a fusion vector such as pGEX (Pharmacia Biotech). The construct is transformed into an appropriate bacterial host, induced, and the fusion protein is purified from the cell lysate by glutathione-Sepharose 4B (Pharmacia Biotech) affinity chromatography.

For in vitro binding assays, cell extracts containing G proteins are prepared by extraction with
35 50 mM Tris, pH 7.8, 1 mM EGTA, 5 mM MgCl₂, 20 mM CHAPS, 20% glycerol, 10 μg of both

aprotinin and leupeptin, and 20 μ l of 50 mM phenylmethylsulfonyl fluoride. The lysate is incubated on ice for 45 min with constant stirring, centrifuged at 23,000 g for 15 min at 4°C, and the supernatant is collected. 750 μ g of cell extract is incubated with glutathione S-transferase (GST) fusion protein beads for 2 h at 4°C. The GST beads are washed five times with phosphate-buffered saline. Bound
5 G protein subunits are detected by [32 P]ADP-ribosylation with pertussis or cholera toxins. The reactions are terminated by the addition of SDS sample buffer (4.6% (w/v) SDS, 10% (v/v) β -mercaptoethanol, 20% (w/v) glycerol, 95.2 mM Tris-HCl, pH 6.8, 0.01% (w/v) bromphenol blue). The [32 P]ADP-labeled proteins are separated on 10% SDS-PAGE gels, and autoradiographed. The separated proteins in these gels are transferred to nitrocellulose paper, blocked with blotto (5% nonfat
10 dried milk, 50 mM Tris-HCl (pH 8.0), 2 mM CaCl₂, 80 mM NaCl, 0.02% NaN₃, and 0.2% Nonidet P-40) for 1 hour at room temperature, followed by incubation for 1.5 hours with Ga subtype selective antibodies (1:500; Calbiochem-Novabiochem). After three washes, blots are incubated with horseradish peroxidase (HRP)-conjugated goat anti-rabbit immunoglobulin (1:2000, Cappel, Westchester PA) and visualized by the chemiluminescence-based ECL method (Amersham Corp.).

15 XVII. Demonstration of GCREC Activity

An assay for GCREC activity measures the expression of GCREC on the cell surface. cDNA encoding GCREC is transfected into an appropriate mammalian cell line. Cell surface proteins are labeled with biotin as described (de la Fuente, M.A. et al. (1997) Blood 90:2398-2405). Immunoprecipitations are performed using GCREC-specific antibodies, and immunoprecipitated
20 samples are analyzed using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of GCREC expressed on the cell surface.

In the alternative, an assay for GCREC activity is based on a prototypical assay for ligand/receptor-mediated modulation of cell proliferation. This assay measures the rate of DNA
25 synthesis in Swiss mouse 3T3 cells. A plasmid containing polynucleotides encoding GCREC is added to quiescent 3T3 cultured cells using transfection methods well known in the art. The transiently transfected cells are then incubated in the presence of [3 H]thymidine, a radioactive DNA precursor molecule. Varying amounts of GCREC ligand are then added to the cultured cells. Incorporation of [3 H]thymidine into acid-precipitable DNA is measured over an appropriate time interval using a
30 radioisotope counter, and the amount incorporated is directly proportional to the amount of newly synthesized DNA. A linear dose-response curve over at least a hundred-fold GCREC ligand concentration range is indicative of receptor activity. One unit of activity per milliliter is defined as the concentration of GCREC producing a 50% response level, where 100% represents maximal incorporation of [3 H]thymidine into acid-precipitable DNA (McKay, I. and I. Leigh, eds. (1993)
35 Growth Factors: A Practical Approach, Oxford University Press, New York NY, p. 73.)

In a further alternative, the assay for GCREC activity is based upon the ability of GPCR family proteins to modulate G protein-activated second messenger signal transduction pathways (e.g., cAMP; Gaudin, P. et al. (1998) J. Biol. Chem. 273:4990-4996). A plasmid encoding full length GCREC is transfected into a mammalian cell line (e.g., Chinese hamster ovary (CHO) or human embryonic kidney (HEK-293) cell lines) using methods well-known in the art. Transfected cells are grown in 12-well trays in culture medium for 48 hours, then the culture medium is discarded, and the attached cells are gently washed with PBS. The cells are then incubated in culture medium with or without ligand for 30 minutes, then the medium is removed and cells lysed by treatment with 1 M perchloric acid. The cAMP levels in the lysate are measured by radioimmunoassay using methods well-known in the art. Changes in the levels of cAMP in the lysate from cells exposed to ligand compared to those without ligand are proportional to the amount of GCREC present in the transfected cells.

To measure changes in inositol phosphate levels, the cells are grown in 24-well plates containing 1×10^5 cells/well and incubated with inositol-free media and [^3H]myoinositol, 2 μCi /well, for 48 hr. The culture medium is removed, and the cells washed with buffer containing 10 mM LiCl followed by addition of ligand. The reaction is stopped by addition of perchloric acid. Inositol phosphates are extracted and separated on Dowex AG1-X8 (Bio-Rad) anion exchange resin, and the total labeled inositol phosphates counted by liquid scintillation. Changes in the levels of labeled inositol phosphate from cells exposed to ligand compared to those without ligand are proportional to the amount of GCREC present in the transfected cells.

XVIII. Identification of GCREC Ligands

GCREC is expressed in a eukaryotic cell line such as CHO (Chinese Hamster Ovary) or HEK (Human Embryonic Kidney) 293 which have a good history of GPCR expression and which contain a wide range of G-proteins allowing for functional coupling of the expressed GCREC to downstream effectors. The transformed cells are assayed for activation of the expressed receptors in the presence of candidate ligands. Activity is measured by changes in intracellular second messengers, such as cyclic AMP or Ca^{2+} . These may be measured directly using standard methods well known in the art, or by the use of reporter gene assays in which a luminescent protein (e.g. firefly luciferase or green fluorescent protein) is under the transcriptional control of a promoter responsive to the stimulation of protein kinase C by the activated receptor (Milligan, G. et al. (1996) Trends Pharmacol. Sci. 17:235-237). Assay technologies are available for both of these second messenger systems to allow high throughput readout in multi-well plate format, such as the adenylyl cyclase activation FlashPlate Assay (NEN Life Sciences Products), or fluorescent Ca^{2+} indicators such as Fluo-4 AM (Molecular Probes) in combination with the FLIPR fluorimetric plate reading system (Molecular Devices). In cases where the physiologically relevant second messenger pathway is not

known, GCREC may be coexpressed with the G-proteins $G_{\alpha 15/16}$ which have been demonstrated to couple to a wide range of G-proteins (Offermanns, S. and M.I. Simon (1995) J. Biol. Chem. 270:15175-15180), in order to funnel the signal transduction of the GCREC through a pathway involving phospholipase C and Ca^{2+} mobilization. Alternatively, GCREC may be expressed in
5 engineered yeast systems which lack endogenous GPCRs, thus providing the advantage of a null background for GCREC activation screening. These yeast systems substitute a human GPCR and G_{α} protein for the corresponding components of the endogenous yeast pheromone receptor pathway. Downstream signaling pathways are also modified so that the normal yeast response to the signal is converted to positive growth on selective media or to reporter gene expression (Broach, J.R. and J.
10 Thorner (1996) Nature 384 (supp.):14-16). The receptors are screened against putative ligands including known GPCR ligands and other naturally occurring bioactive molecules. Biological extracts from tissues, biological fluids and cell supernatants are also screened.

Various modifications and variations of the described methods and systems of the invention
15 will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the
20 following claims.

Table 1

Incyte Project ID	Polypeptide SEQ ID NO:	Incyte Polypeptide ID	Polynucleotide SEQ ID NO:	Incyte Polynucleotide ID
2536292	1	2536292CD1	17	2536292CB1
7477708	2	7477708CD1	18	7477708CB1
7474823	3	7474823CD1	19	7474823CB1
644692	4	644692CD1	20	644692CB1
3837054	5	3837054CD1	21	3837054CB1
6157025	6	6157025CD1	22	6157025CB1
55012817	7	55012817CD1	23	55012817CB1
7475061	8	7475061CD1	24	7475061CB1
7477374	9	7477374CD1	25	7477374CB1
7479890	10	7479890CD1	26	7479890CB1
7482825	11	7482825CD1	27	7482825CB1
7483087	12	7483087CD1	28	7483087CB1
7483134	13	7483134CD1	29	7483134CB1
7478550	14	7478550CD1	30	7478550CB1
7483142	15	7483142CD1	31	7483142CB1
7483151	16	7483151CD1	32	7483151CB1

Table 2

Polypeptide SEQ ID NO:	Incyte Polypeptide ID	GenBank ID NO:	Probability Score	GenBank Homolog
1	2536292CD1	g1039470	8.1E-07	[Rattus norvegicus] pheromone receptor VN1 (Dulac, C. and R. Axel (1996) Cell 83:195-206)
2	7477708CD1	g5525078	1.2E-89	[Rattus norvegicus] seven transmembrane receptor (Abe, J. et al. (1999) J. Biol. Chem. 274:19957-19964)
3	7474823CD1	g10241847	6.0E-79	[Homo sapiens] histamine H4 receptor (Oda, T. et al. (2000) J. Biol. Chem. 275:36781-36786)
4	644692CD1	g2117161	3.2E-35	[Homo sapiens] seven transmembrane-domain receptor (Osterhoff, C. et al. (1997) DNA Cell Biol. 16:379-389)
5	3837054CD1	g1902964	7.1E-21	[Mus sp.] oxytocin receptor (Kubota, Y. (1996) Mol. Cell. Endocrinol. 124:25-32)
6	6157025CD1	g5359718	2.5E-21	[Homo sapiens] cysteinyl leukotriene receptor (Sarau, H.M. et al. (1999) Mol. Pharmacol. 56:657-663)
7	55012817CD1	g6006811	8.6E-60	[Mus musculus] serpentine receptor
8	7475061CD1	g440626	2.2E-22	[Astyax mexicanus] opsin
9	7477374CD1	g14600082	0.0	[Homo sapiens] trace amine receptor 3 (Borowsky, B. et al. (2001) Proc. Natl. Acad. Sci. USA 98:8966-8971)
10	7479890CD1	g10441732	0.0	[Homo sapiens] leucine-rich repeat-containing G protein-coupled receptor 6
11	7482825CD1	g4680254	1.3E-68	(Hsu, S.Y. et al. (2000) Mol. Endocrinol. 14:1257-1271)
12	7483087CD1	g5901488 g2792018	1.5E-101 8.4E-99	[Mus musculus] odorant receptor S1 (Hirono, M.B. et al. (1999) Cell 96:713-723)
13	7483134CD1	g6178008	8.3E-92	[Marmota marmota] olfactory receptor (Homo sapiens] olfactory receptor (Vanderhaeghen, P. et al. (1997) Biochem. Biophys. Res. Commun. 237:283-287)
14	7478550CD1	g3983394	1.2E-53	[Mus musculus] odorant receptor MOR18 (Tsuboi, A. et al. (1999) J. Neurosci. 19:8409-8418)
15	7483142CD1	g1246534	1.1E-91	[Mus musculus] olfactory receptor F7 (Krautwurst, D. et al. (1998) Cell 95:917-926)
16	7483151CD1	g1246532	1.9E-78	[Gallus gallus] olfactory receptor 4 (Leibovici, M. et al. (1996) Dev. Biol. 175:118-131)
				[Gallus gallus] olfactory receptor 3 (Leibovici, M. et al. (1996) Dev. Biol. 175:118-131)

Table 3 (cont.)

SEQ ID NO:	Incyte Polypeptide ID	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Domains and Motifs	Analytical Methods and Databases
6	6157025CD1	339	T6 S10 Y175 S217 S276 S332	N5 N9 N308	G-PROTEIN COUPLED RECEPTORS: DM00013 P34993 36-327: L20-F285 DM00013 P30872 52-338: L20-F285 G-protein coupled receptor BL00237: H218-F244, N9-F25, W81-C120 Transmembrane domain: I21-M45, V43-S63, M99-I116, M139-Y155, I185-V208, N227-L249	BLAST-DOMO BLIMPS-BLOCKS HMMER
7	55012817CD1	549	S19 S57 T103 T153 T224 T3 T407 T415 T537 T84	N144 N210 N413 N98	Signal peptide: M1-G20 Signal peptide: M1-E22 Transmembrane domains: G499-I523, L477-F495, H436-F458, Y378-L405, A274-L293 7 transmembrane receptor (Secretin family): V265-S528 G-protein coupled receptor BL00649: M280-V325, C338-L363, G386-D410, Y429-F458, N472-A493 Secretin-like GPCR superfamily PR00249: R270-R294, A340-L363, F379-G404, L492-I517, K475-F495, V503-L524 EMR1 leucocyte antigen: DM05221 I37225 347-738: P207-I517 DM05221 P48960 347-738: P207-I517 DM05221 A57172 465-886: L177-I517 G-protein coupled receptor PD000752: I271-L524	SPScan HMMER HMMER HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-DOMO
8	7475061CD1	188	S163 S179 S64 T159 T174		Signal peptide: M1-I50 Transmembrane domains: F34-F52, M90-F112	BLAST-PRODOR SPScan HMMER

Table 6 (cont.)

Library	Vector	Library Description
DENDTNT01	pINCY	Library was constructed using RNA isolated from treated dendritic cells from peripheral blood.
LUNGNON07	pINCY	This normalized lung tissue library was constructed from 5.1 million independent clones from a lung tissue library. Starting RNA was made from RNA isolated from lung tissue. The library was normalized in two rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228-9232 and Bonaldo et al., Genome Research (1996) 6:791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
MONOTXN05	pINCY	This normalized treated monocyte cell tissue library was constructed from 1.03 million independent clones from a monocyte tissue library. Starting RNA was made from RNA isolated from treated monocytes from peripheral blood removed from a 42-year-old female. The cells were treated with interleukin-10 (IL-10) and lipopolysaccharide (LPS). The library was normalized in two rounds using conditions adapted from Soares et al., PNAS (1994) 91:9228-9232 and Bonaldo et al., Genome Research 6 (1996):791, except that a significantly longer (48 hours/round) reannealing hybridization was used.
SINTTMR02	PCDNA2.1	This random primed library was constructed using RNA isolated from small intestine tissue removed from a 59-year-old male. Pathology for the matched tumor tissue indicated multiple (9) carcinoid tumors, grade 1, in the small bowel. The largest tumor was associated with a large mesenteric mass. Multiple convoluted segments of bowel were adhered to the tumor. A single (1 of 13) regional lymph node was positive for malignancy. The peritoneal biopsy indicated focal fat necrosis.
UCMCL5T01	PBLUESCRIPT	Library was constructed using RNA isolated from mononuclear cells obtained from the umbilical cord blood of 12 individuals. The cells were cultured for 12 days with IL-5 before RNA was obtained from the pooled lysates.

1. An isolated polypeptide selected from the group consisting of:
 - a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-16,
 - b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-16,
 - c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and
 - d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.
2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-16.
3. An isolated polynucleotide encoding a polypeptide of claim 1.
4. An isolated polynucleotide encoding a polypeptide of claim 2.
5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:17-32.
6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
7. A cell transformed with a recombinant polynucleotide of claim 6.
8. A transgenic organism comprising a recombinant polynucleotide of claim 6.
9. A method of producing a polypeptide of claim 1, the method comprising:
 - a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and
 - b) recovering the polypeptide so expressed.

10. A method of claim 9, wherein the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.

11. An isolated antibody which specifically binds to a polypeptide of claim 1.

5

12. An isolated polynucleotide selected from the group consisting of:

- a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:17-32,
- b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:17-32,
- c) a polynucleotide complementary to a polynucleotide of a),
- d) a polynucleotide complementary to a polynucleotide of b), and
- e) an RNA equivalent of a)-d).

15

13. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 12.

14. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 12, the method comprising:

- a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and
- b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

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15. A method of claim 14, wherein the probe comprises at least 60 contiguous nucleotides.

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16. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 12, the method comprising:

- a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and
- b) detecting the presence or absence of said amplified target polynucleotide or fragment

35

thereof, and, optionally, if present, the amount thereof.

17. A composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

5

18. A composition of claim 17, wherein the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.

19. A method for treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment the composition of claim 17.

20. A method of screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- 15
- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
 - b) detecting agonist activity in the sample.

21. A composition comprising an agonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

20

22. A method for treating a disease or condition associated with decreased expression of functional GCREC, comprising administering to a patient in need of such treatment a composition of claim 21.

23. A method of screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- 25
- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
 - b) detecting antagonist activity in the sample.

24. A composition comprising an antagonist compound identified by a method of claim 23 and a pharmaceutically acceptable excipient.

30

25. A method for treating a disease or condition associated with overexpression of functional GCREC, comprising administering to a patient in need of such treatment a composition of claim 24.

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26. A method of screening for a compound that specifically binds to the polypeptide of claim 1, the method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- 5 b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

27. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, the method comprising:

- 10 a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and
- 15 c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

28. A method of screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,
- 25 b) detecting altered expression of the target polynucleotide, and
- c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

29. A method of assessing toxicity of a test compound, the method comprising:

- 30 a) treating a biological sample containing nucleic acids with the test compound,
- b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 12 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a
- 35 polynucleotide sequence of a polynucleotide of claim 12 or fragment thereof,

- c) quantifying the amount of hybridization complex, and
- d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

30. A diagnostic test for a condition or disease associated with the expression of GCREC in a biological sample, the method comprising:

- a) combining the biological sample with an antibody of claim 11, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex, and
- b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

31. The antibody of claim 11, wherein the antibody is:

- a) a chimeric antibody,
- b) a single chain antibody,
- c) a Fab fragment,
- d) a F(ab')₂ fragment, or
- e) a humanized antibody.

32. A composition comprising an antibody of claim 11 and an acceptable excipient.

33. A method of diagnosing a condition or disease associated with the expression of GCREC in a subject, comprising administering to said subject an effective amount of the composition of claim 32.

34. A composition of claim 32, wherein the antibody is labeled.

35. A method of diagnosing a condition or disease associated with the expression of GCREC in a subject, comprising administering to said subject an effective amount of the composition of claim 34.

36. A method of preparing a polyclonal antibody with the specificity of the antibody of claim

11, the method comprising:

- a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibodies from said animal, and
- c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.

37. A polyclonal antibody produced by a method of claim 36.

38. A composition comprising the polyclonal antibody of claim 37 and a suitable carrier.

39. A method of making a monoclonal antibody with the specificity of the antibody of claim

11, the method comprising:

- a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibody producing cells from the animal,
- c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells,
- d) culturing the hybridoma cells, and
- e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.

40. A monoclonal antibody produced by a method of claim 39.

41. A composition comprising the monoclonal antibody of claim 40 and a suitable carrier.

42. The antibody of claim 11, wherein the antibody is produced by screening a Fab expression library.

43. The antibody of claim 11, wherein the antibody is produced by screening a recombinant

immunoglobulin library.

44. A method of detecting a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16 in a sample, the method comprising:

- 5 a) incubating the antibody of claim 11 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16 in the sample.

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45. A method of purifying a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16 from a sample, the method comprising:

- a) incubating the antibody of claim 11 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- 15 b) separating the antibody from the sample and obtaining the purified polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.

46. A microarray wherein at least one element of the microarray is a polynucleotide of claim 13.

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47. A method of generating a transcript image of a sample which contains polynucleotides, the method comprising:

- a) labeling the polynucleotides of the sample,
- b) contacting the elements of the microarray of claim 46 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and
- 25 c) quantifying the expression of the polynucleotides in the sample.

48. An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises a first oligonucleotide or polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 12.

49. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is

completely complementary to at least 30 contiguous nucleotides of said target polynucleotide.

50. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to at least 60 contiguous nucleotides of said target polynucleotide.

5

51. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to said target polynucleotide.

52. An array of claim 48, which is a microarray.

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53. An array of claim 48, further comprising said target polynucleotide hybridized to a nucleotide molecule comprising said first oligonucleotide or polynucleotide sequence.

54. An array of claim 48, wherein a linker joins at least one of said nucleotide molecules to said solid substrate.

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55. An array of claim 48, wherein each distinct physical location on the substrate contains multiple nucleotide molecules, and the multiple nucleotide molecules at any single distinct physical location have the same sequence, and each distinct physical location on the substrate contains nucleotide molecules having a sequence which differs from the sequence of nucleotide molecules at another distinct physical location on the substrate.

20

56. A method of identifying a compound that modulates, mimics and/or blocks an olfactory and/or taste sensation, the method comprising:

25

- a) contacting the compound with an olfactory and/or taste receptor polypeptide selected from the group consisting of:
 - i) a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16,
 - ii) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-16, and
 - iii) an olfactory and/or taste receptor having an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-16.
- b) identifying whether the compound specifically binds to and/or affects the activity of

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said receptor polypeptide.

57. The method of claim 56, wherein said receptor polypeptide is expressed on the surface of a mammalian cell.

5

58. The method of claim 57, wherein said mammalian cell expresses a G-protein.

59. The method of claim 58, wherein said mammalian cell expresses a plurality of G-protein coupled receptors.

10

60. The method of claim 59, wherein said mammalian cell expresses another olfactory and/or taste receptor polypeptide.

61. The method of claim 56, wherein said receptor polypeptide is fused to another polypeptide.

15

62. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

63. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:2.

20

64. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:3.

65. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:4.

25

66. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:5.

67. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:6.

68. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:7.

30

69. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:8.

70. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:9.

71. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:10.

72. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:11.

5 73. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:12.

74. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:13.

10 75. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:14.

76. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:15.

77. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:16.

15 78. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:17.

79. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:18.

20 80. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:19.

81. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:20.

82. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:21.

25 83. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:22.

84. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:23.

30 85. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:24.

86. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:25.

87. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:26.

88. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:27.

89. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:28.

5 90. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:29.

91. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:30.

92. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:31.

10

93. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:32.

PI-0236 PCT

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PI-0236 PCT

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